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10/520,026	02/14/2006	Zhenping Zhu	11245/48503	7237
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Lerner, David, Littenberg, Krumholz & Mentlik, LLP			HUYNH, PHUONG N	
600 South Avenue West				
Westfield, NJ 07090			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/520,026

Applicant(s)

ZHU, ZHENPING

Examiner

PHUONG HUYNH

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 April 2009.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-43 is/are pending in the application.
4a) Of the above claim(s) 1-40 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 41-43 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 12/27/04 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/IS/C)
Paper No(s)/Mail Date See Continuation Sheet
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/28/09; 2/28/09; 2/28/09; 1/17/06.

DETAILED ACTION

1. Claims 1-43 are pending.
2. Applicant's election of Group VII in the reply filed on April 21, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
3. Claims 1-40 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 41-43, drawn to a method for neutralizing activation of a first VEGF receptor and a second VEGF receptor in a cell, a method of reducing tumor growth in a mammal in need thereof, and a method for inhibiting angiogenesis in a mammal in need thereof which comprises treating a cell with an antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount sufficient to neutralize activation of the receptors wherein the first receptor is KDR and the second receptor is Flt-1 that read on the disclosed combination of six CDRs for heavy chain and light chain (SEQ ID NO: 1-6) which correspond to the first VEGF receptor KDR, and SEQ ID NO: 35-40 which correspond to the second VEGFR, Flt-1, are being acted upon in this Office Action.
5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for neutralizing activation of KDR receptor and Flt-1 receptor in a cell which comprises treating a cell with a single chain bifunctional diabody having a first antigen binding site specific for human VEGFR1 (also known as Flt-1) and a second binding site specific for a human VEGFR2 (also known as KDR), **does not** reasonably provide enablement for any of the method as set forth in claims 41-43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claim 41 is broadly drawn to a method for neutralizing activation of any first VEGF receptor and any second VEGF receptor in any cell which comprises treating said cell with any antibody having a first antigen binding site specific for any first VEGF receptor and a second binding site specific for any second VEGF receptor.

Claim 42 is broadly drawn to a method for reducing tumor growth in all mammals in need thereof comprising treating such mammal with any antibody having a first antigen binding site specific for any first VEGF receptor and a second binding specific for any second VEGF receptor in an amount effective to reduce tumor growth.

Claim 43 is broadly drawn to a method for inhibiting angiogenesis in all mammals in need thereof comprising treating such mammal with any bispecific antibody having any first antigen binding site specific for any first VEGF receptor and any second binding specific for any second VEGF receptor in an amount effective to reduce tumor growth.

Enablement is not commensurate in scope with how to make and use all antibodies having any antigen binding site specific for any first VEGF receptor and any second binding site

specific for any second VEGF receptor for a method of reducing tumor growth in all mammals or inhibiting angiogenesis in all mammals.

The specification discloses only one single chain bifunctional diabody that capable of binding both of its targets human VEGF receptors KDR and Flt-1 simultaneously, see pages 30 and 32. The diabody inhibits VEGF and PlGF induced cell migration of leukemia cells HL60, and HEL in dose dependent manner *in vitro*, see page 33. The specification discloses combination of both scFv pIC11 and scFv 6.12 either as a simple mixture or in the diabody format demonstrated a more potent inhibitory effect than either scFv alone, see page 34. The specification discloses a method of how to assemble the bispecific diabody from scFv antibody, see page 29. Based on just one *in vitro* working example, applicant postulate any bispecific antibody that binds to any two VEGFRs is effective in treating any and all tumors in all mammals.

At the time of filing, there is no showing of any and all antibody having a first antigen binding site specific for any first VEGF receptor and a second antigen binding site specific for any second receptor is effective for reducing any tumor growth in all mammal or inhibiting angiogenesis in all mammal. First, there is insufficient guidance as to the structure associated with the binding specificity of the immunoglobulin heavy and light chains CDRs for all bispecific antibody having a first and a second antigen binding sites for any all VEGF receptors. Second, there is a lack of *in vivo* working example to show any unspecified bispecific diabody even bind to VEGFRs among the VEGF receptors from all mammals. Third, even if the precise structure of the immunoglobulin heavy and light chains CDRs that binds to human VEGFR is known, it is unpredictable such antibody binds to all VEGFR from all mammals. The state of the art at the time of filing as exemplified by Witte et al (Cancer and Metastasis Reviews 17: 155-161, 1998; PTO 892) is such that antibody that binds to human VEGFR2 (KDR) fails to bind to mouse VEGFR despite the mouse and human VEGFR have high sequence identity. Monoclonal antibody such as DC 101 that binds to mouse VEGFR2 and blocks the binding of VEGF to its receptor; the same antibody does not even binds to VEGFR2 or KDR from other mammal such as human, see abstract, in particular.

Finally, given the innumerable bispecific antibody, the unpredictability of such antibody to treat any and all tumor in all mammals, the specification does not teach how to extrapolate data obtained from *in vitro* binding inhibition assays or cell migration to the development of effective *in vivo* human therapeutic compositions, commensurate in scope with the claimed methods.

Given the lack of guidance as to binding specificity associated with the structure of six CDRs of all antibody, the lack of direction and *in vivo* working examples, the breadth of the claims, which encompass innumerable possible antibodies, VEGFRs and mammals, and the amount of experimentation required to determine each possible species individually for reducing any tumor growth in all mammals, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In *re wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 41 is broadly drawn to a method for neutralizing activation of any first VEGF receptor and any second VEGF receptor in any cell which comprises treating said cell with any antibody having a first antigen binding site specific for any first VEGF receptor and a second binding site specific for any second VEGF receptor.

Claim 42 is broadly drawn to a method for reducing tumor growth in all mammals in need thereof comprising treating such mammal with any antibody having a first antigen binding site specific for any first VEGF receptor and a second binding site specific for any second VEGF receptor in an amount effective to reduce tumor growth.

Claim 43 is broadly drawn to a method for inhibiting angiogenesis in all mammals in need thereof comprising treating such mammal with any bispecific antibody having any first antigen binding site specific for any first VEGF receptor and any second binding site specific for any second VEGF receptor in an amount effective to reduce tumor growth.

The specification describes only one anti-KDR and Flt-1 bifunctional diabody that capable of binding both of its targets KDR and Flt-1 simultaneously, see pages 30 and 32. The diabody inhibits VEGF and PlGF induced cell migration of leukemia cells HL60, and HEL in dose dependent manner in vitro, see page 33. The specification discloses combination of both scFv pIC11 and scFv 6.12 either as a simple mixture or in the diabody format demonstrated a more potent inhibitory effect than either scFv alone, see page 34. The specification discloses a method of how to assemble the bispecific diabody from scFv antibody, see page 29.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116.).

At the time of filing, Applicant is not in possession of any and all antibody having a first antigen binding specific for any first VEGF receptor and a second antigen binding site specific for any second receptor for the claimed methods for reducing any tumor growth in all mammal or inhibiting angiogenesis in all mammal. The structure of the immunoglobulin heavy and light chains CDRs of all bispecific antibody having a first and a second antigen binding sites for all VEGF receptors associated with binding specificity and function has not been adequately described. Further, there is disclosure as to any bispecific diabody that even binds to all mammalian VEGFRs for the claimed methods of reducing tumor growth or inhibiting angiogenesis in all mammals.

Even if the precise structure of the immunoglobulin heavy and light chains CDRs that binds to human VEGFR is known, it is unpredictable such antibody binds to any VEGFR from all mammals. The state of the art at the time of filing as exemplified by Witte et al (Cancer and Metastasis Reviews 17: 155-161, 1998; PTO 892) is such that antibody that binds to human VEGFR2 (KDR), the same antibody does not bind to mouse VEGFR. Monoclonal antibody such as DC 101 that binds to mouse VEGFR2 and blocks the binding of VEGF to its receptor; the same antibody does not even binds to VEGFR2 or KDR from other mammal such as human, see abstract, in particular.

Further, given the innumerable bispecific antibodies, the unpredictability of such antibody to treat any and all tumor in all mammals, the specification does not adequately teach how to effectively reducing any tumor, any angiogenesis disease or reaching any therapeutic endpoint in humans by administering any unspecified bispecific antibody. The specification does not describe how to extrapolate data obtained from *in vitro* binding inhibition assays or migration assays to the development of effective *in vivo* human therapeutic compositions, commensurate in scope with the claimed methods.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factor to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., complete or partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, method of making the claimed invention, level of skill and knowledge in the art and predictability in the art sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF’s were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification discloses only one bispecific diabody that binds to human KDR and human Flt-1 made from scFv pIC11 that binds to human KDR and scFv 6.12 that binds to human Flt-1 and neutralizes activation of said receptors by VEGF *in vitro*.

Because the described bispecific diabody that binds to human KDR and human Flt-1 is not representative of the entire claimed genus as this antibody does not bind to any mammalian VEGFRs and the specification does not describe the structural features shared by members of the genus, one of skill in the art would conclude that applicant was not in possession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 41-43.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 <http://www.USPTO.gov/web/menu/written.pdf>.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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10. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanno et al (Oncogene 19: 2138-2146, 1998; PTO 1449) in view of WO 00/44777 (published August 2000, PTO 1449) and/or Lu et al (Cancer Res 58: 3209-3214, Aug 1998; PTO 1449).

Kanno et al teach a method of neutralizing activation of Flt-1 and KDR in endothelial cell comprising treating such cell with an antibody such as KM1750 having a first antigen binding site specific for Flt-1 (VEGFR1) and a second antibody having a binding site specific for KDR (VEGFR2), see page 3b, in particular. Kanno et al further teaches that anti-KDR antibody inhibits VEGF mediated human endothelial cell DNA synthesis while anti-Flt1 antibody inhibits VEGF mediated cell migration (see abstract, in particular).

The invention in claim 41 differs from the teachings of the reference only in that the method wherein the antibody is a bispecific antibody instead of two antibodies each having a first antigen binding site specific for said first VEGF receptor and a second binding site specific for any second VEGF receptor.

The WO 00/44777 publication teaches a method for neutralizing the activation of VEGFR2 such as KDR by administering to a mammal an effective of a single chain antibody such as diabody comprising a binding site having a first antigen binding site specific for a first VEGF receptor such as human KDR (VEGFR-2) and a second binding site specific for another antigen (see claims 51 of the WO 00/44777 publication, page 8, line 7-10, in particular). The WO 00/44777 publication teaches a method of reducing tumor growth and a method of inhibiting angiogenesis by administering to a mammal an effective amount of a diabody that binds to KDR that neutralizes the activation of KDR (see claims 52-53, 55-57, 59-61, in particular). The WO 00/44777 publication teaches a method of making such bispecific single chain antibody (see pages 8-9, claims 46, 54, in particular). The reference antibody effective inhibits VEGF-stimulated phosphorylation of KDR receptor (see pages 17 and 24, in particular), inhibits VEGF-stimulated mitogenesis of human endothelial cells (see page 24, line 20, in particular).

Lu et al teach bispecific antibodies have been exploited both in cancer immunodiagnostic and cancer therapies (see page 159, col. 2, in particular). Lu et al teach a method of making a single chain bispecific diabody such as pDAB34 having a first antigen binding site specific for a first VEGF receptor such as human KDR (VEGFR-2) located to an epitope on KDR extracellular domain (ECD) Ig domain 1 and a second antigen binding site specific for a second VEGF receptor such as human VEGFR2/KDR Ig ECD Ig domains 6 and 7 (see page 160, col. 2, last paragraph, page 161, construction of diabody pDAB34, Figure 1A, in particular). Lu et al teach a

method of making the reference bispecific diabody, which method comprises coexpressing in a host cell such as *E. coli* strain HB2151 a recombinant DNA construct such as a plasmid such as scFv p3S5 encoding a first polypeptide having the first immunoglobulin heavy chain variable domain (VH) of p3S5 located to the N-terminus of the second immunoglobulin light chain variable domain (VL) such as scFv p4G7 and a recombinant DNA construct encoding a second polypeptide having the second heavy chain variable domain such as scFv p4G7 VH domain located to the N-terminus of the first immunoglobulin light chain variable domain such as scFv p3S5VL domain and express the diabody in *E. coli* cell for a time and in a manner sufficient to allow expression of the polypeptide and the formation of the diabody that binds to the first VEGFR such as human VEGFR2/KDR extracellular domain (ECD) Ig domain 1 and the second VEGF receptor such as human VEGFR2/KDR ECD Ig domains 6 and 7 (see page 161, construction of diabody pDAB34, Figure 1A, in particular). Lu et al teach the method of making bispecific diabody with acquired antagonist activity, effectively blocking VEGF receptor KDR/VEGF interaction (see abstract, paragraph bridging pages 160 and 161, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to neutralize the activation of both VEGF receptors Flt1 and KDR of Kanno et al by substituting one of the antigen binding site that binds to KDR in the single chain bispecific diabody having both antigen sites that binds to different epitope KDR as taught by WO 00/44777 publication or Lu et al to form a bispecific diabody having a first antigen binding site specific a first VEGF receptor such as KDR and a second binding site specific for a second VEGF receptor such as Flt-1 for neutralizing activation of both VEGF receptors, reducing tumor growth and/or inhibits angiogenesis in a mammal as taught by the WO 00/44777 publication or Lu et al.

One having ordinary skill in the art would have been motivated with the expectation of success to substitute one of the antigen binding site for another antigen binding site to form a bispecific antibody because Lu et al teach bispecific antibodies have been shown promise in treatment and diagnosis of cancer (see page 159, col. 2, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to substitute one of the antigen binding site for another antigen binding site to form a bispecific antibody that binds to two different epitopes because bispecific single chain antibody allows for the recognition of two different epitopes one on each VEGF receptors such as KDR

and other as taught by the WO 00/44777 publication (see page 8, lines 7-10, in particular) and useful for treating tumor or inhibiting angiogenesis by neutralizing the activation of VEGFR (KDR) by VEGF (see claims 52-53, 55-57, 59-61, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to substitute one of the antigen binding site for another antigen binding site to form a bispecific antibody because anti-KDR antibody inhibits VEGF mediated human endothelial cell DNA synthesis while anti-Flt1 antibody inhibits VEGF mediated cell migration as taught by Kanno et al (see abstract, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

- A) Combining prior art elements according known methods to yield predictable results.
- B) Simple substitution of one known element for another to obtain predictable results.
- C) Use of known technique to improve similar products in the same way.
- D) Applying known technique to a known product ready for improvement to yield predictable results.
- E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.
- F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since bispecific antibodies have shown promise in cancer therapy and immunodiagnostic, simple substitution of one known element such as one antigen binding site KDR for another antigen binding site that binds to Flt-1 to obtain bispecific antibody that binds to KDR and Flt-1 with predictable results. Further, applying known technique as taught by Lu et al or WO 00/44777 to a known product as taught by Kanno et al ready for improvement to yield predictable bispecific single chain antibody for cancer therapy.

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11. Antibody that binds to KDR comprising the specific combination of CDRs1-6 as set forth in SEQ ID NO: 35-40 are free of prior art.
12. No claim is allowed.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.
14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644

June 19, 2009